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## **2016 European Guideline on the management of non-gonococcal urethritis**

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**Key words:** Chlamydia (Chlamydia trachomatis), NGU (Non-gonococcal urethritis)

### **Guideline Development**

This guideline has been updated by reviewing the previous UK and European non-gonococcal urethritis (2009) guidelines and UK 2015 guideline and conducting a comprehensive literature search of publications from 2008 to September 2015.

## Abstract

We present the updated International Union against Sexually Transmitted Infections (IUSTI) guideline for the management of non-gonococcal urethritis in men. This guideline recommends confirmation of urethritis in symptomatic men before starting treatment. It does not recommend testing asymptomatic men for the presence of urethritis. All men with urethritis should be tested for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* and ideally *M. genitalium* using a NAAT as this is highly likely to improve clinical outcomes. If a NAAT is positive for gonorrhoea, a culture should be performed before treatment. In view of the increasing evidence that azithromycin 1 g may result in the development of antimicrobial resistance in *Mycoplasma genitalium* azithromycin 1 g is no longer recommended as first line therapy which should be doxycycline 100mgs bd for 7 days. If azithromycin is to be prescribed an extended of 500mg then 250mg daily for 4 days is to be preferred over 1g stat. In men with persistent NGU, *M. genitalium* NAAT testing is recommended if not previously undertaken, as is *Trichomonas vaginalis* NAAT testing in populations where *T. vaginalis* is detectable in >2% of symptomatic women.

## What is new in this updated guideline?

### Diagnosis

- Urethritis should be confirmed by urethral smear microscopy in symptomatic patients
- Symptoms and negative urethral smear
  - No empirical treatment. Re-attend for early morning smear if negative NAATs and symptoms do not settle

### Investigations

- All men assessed for STIs, regardless of symptoms, should be tested for *C. trachomatis* from a FVU specimen and for *N. gonorrhoeae* if they have urethritis. If a NAAT is positive for gonorrhoea, a culture should be performed before treatment.
- All men who have sex with men should be tested for both *C. trachomatis* and *N. gonorrhoeae* from any potentially exposed site.
- Testing male patients with urethritis for *M. genitalium*, preferably with screening for macrolide resistance, is highly likely to improve clinical outcomes.

### Management

- Recommended syndromic regimen: doxycycline 100mgs twice daily for seven days.
  - *Azithromycin 1 gram stat should not be used routinely because of the increased risk of inducing macrolide antimicrobial resistance with M. genitalium*
- If *M. genitalium*-positive: azithromycin 500mgs stat, then 250 mg od for 4 days.
  - A test of cure 3-5 weeks after treatment in those who tested positive for *M. genitalium* should be performed.

### Persistent/Recurrent NGU

- Consider testing for *M. genitalium* using a NAAT preferably with screening for macrolide resistance.
- Consider testing for *Trichomonas vaginalis* using a NAAT if it is prevalent in the local population (>2% in symptomatic women).
- Only treat if patient has definite symptoms of urethritis, or physical signs on examination AND microscopic evidence of urethritis.

## Introduction

Urethritis, or inflammation of the urethra, is a multifactorial condition which is sexually acquired in the majority of cases. It is characterised by discharge, dysuria and/or urethral discomfort but may be asymptomatic. The diagnosis of urethritis is confirmed by demonstrating an excess of polymorphonuclear leukocytes (PMNLs) in the anterior urethra. This is usually assessed using a urethral smear but a first void urine specimen (FVU) can also be used. Urethritis is described as either gonococcal, when *Neisseria gonorrhoeae* is detected, or non-gonococcal (NGU) when it is not. The term nonspecific urethritis (NSU) applies to non-gonococcal non-chlamydial urethritis and in order to prevent confusion should be avoided.

There are a number of uncertainties with NGU. There is significant inter-observer and intra-observer error in performing and reading urethral slides and counting PMNLs, especially in samples with low grade inflammation.<sup>1,2</sup> In many men with urethritis a known pathogen is not detected.<sup>3-13</sup>

## Aetiology

The prevalence of the common organisms associated with NGU in more recent studies is listed in table 1.

The commonest organisms implicated are *C. trachomatis* and *M. genitalium*, with the latter perhaps causing more symptoms.<sup>4,5</sup> Chlamydia and *M. genitalium* are more likely to be detected in:

- Younger patients with NGU, although this association is not as strong for *M. genitalium*.<sup>3,5,6</sup>
- Those with a urethral discharge and/or dysuria.<sup>3,6,7,14</sup>
- *C. trachomatis* and *M. genitalium* may be less common in men who have sex with men (MSM) than heterosexual men with NGU.<sup>15</sup>
- *M. genitalium* has been associated with balano-posthitis and *C. trachomatis* with a circinate balanitis.<sup>16,17</sup>
- The two organisms only infrequently coexist in the same individual with NGU<sup>18</sup>, but dual infections have been identified in up to 10% of men in some studies.<sup>3,19</sup>

- Men with a urethral discharge have a higher bacterial load than those without urethritis.<sup>20,21</sup>

In 30-80% of the cases with NGU neither *C. trachomatis* nor *M. genitalium* is detected.<sup>3-12</sup>

- The isolation of *Trichomonas vaginalis* is dependent on the prevalence of the organism in the community (22-28).
- There is good evidence that *U. urealyticum* causes urethritis in some men but not all men.<sup>22</sup> Detection even using a nucleic acid amplification test( NAAT) *cannot* distinguish between asymptomatic carriage and possible causality.<sup>22</sup> The immune response may influence the development of NGU.<sup>23</sup> Also, higher organism load (>1000 copies/ml of FVU) is a stronger predictor of NGU.<sup>24,25</sup>
  - Earlier studies did not differentiate between the two species *Ureaplasma urealyticum* (biovar 2) and *U. parvum* (biovar 1) which continues to be the case *if culture alone* is used.<sup>22</sup> *U. parvum* is detected more often in controls than cases which probably explains why earlier studies failed to demonstrate a consistent association of ureaplasmas with NGU.<sup>22</sup>
- There is increasing evidence that bacterial vaginosis-associated bacteria may cause NGU.<sup>26-28</sup>
- If urinary tract infection is found, young men should be investigated for urinary tract abnormalities.<sup>29</sup>
- Adenoviruses or Herpes simplex viruses types 1 and 2 may account for 2-4% of symptomatic patients and this may be associated with conjunctivitis.<sup>8,30,31</sup>
- *N. meningitidis*, *Haemophilus sp.*, *Candida sp.*, urethral stricture and foreign bodies probably account for a small proportion of NGU, whilst the role of Epstein Barr Virus is questionable.<sup>32,33</sup>
- What causes organism negative NGU or idiopathic urethritis is unclear. Some of these cases are almost certainly non-infective, but we do not currently have the tools to be able to differentiate probably non-infective from likely infective cases.<sup>34</sup>

Asymptomatic urethritis, without an observable discharge, probably has a different aetiology from symptomatic urethritis, with *C. trachomatis* and *M. genitalium* being detected less frequently.<sup>4,5,7,35</sup>

**This guideline does not recommend testing asymptomatic men with urethral microscopy for non-gonococcal urethritis. (III, B)**

## **Clinical features**

### **SYMPTOMS**

- Urethral discharge
- Dysuria
- Penile tip irritation
- Urethral discomfort and/or itch
- Nil

### **SIGNS**

- Urethral discharge.
- Penile tip erythema
- Normal examination

### **COMPLICATIONS**

- Epididymo-orchitis
- Sexually acquired reactive arthritis – acute or chronic

### **Diagnosis**

Symptomatic patients and those with a visible discharge should be assessed for the presence of urethritis. (IV, C)

Urethritis should be confirmed by demonstrating PMNLs from the anterior urethra using a Gram stained or methylene-blue stained urethral smear, which should contain  $\geq 5$  PMNL per high power (hpf) (x1000) microscopic field (averaged over five fields with greatest concentration of PMNLs).<sup>4,36,37</sup>

- The quality of the smear is heavily dependent on how the smear is taken and there is both inter and intra-observer variation when interpreting the result.<sup>1,2</sup>

Either a 5 mm plastic loop or cotton tipped swab can be used, which should be introduced about 1 cm into the urethra.<sup>38</sup> (1b) Other methods are also used, including a sterile blunt curette or spatula.<sup>39</sup> (C)

- Based on reported sensitivities of microscopy for detection of chlamydia, blunt curette is more sensitive than a loop which is better than a swab.<sup>4,39-41</sup> (III)
- If a urethral discharge is present the smear can be sampled without placing the device inside the meatus.<sup>38</sup> (IV, C)
- A viral aetiology is likely if the leukocytes are predominantly mononuclear.<sup>31</sup>

An FVU specimen can be examined for threads and if present these can be stained and interpreted as for a spun deposit ( $\geq 10$  PMNL/hpf indicates urethritis).<sup>11,42</sup> (III, B)

### **Management of symptomatic patients with a negative urethral smear**

- If the urethral smear is normal the patient can be reassured and advised to re-attend for an early morning smear if his symptoms do not settle. He should be advised to hold his urine overnight and to attend not having voided urine. It is good practice to advise the patient to take their last drink at about 8 pm and to void about 3 hours later in order to help avoid waking with a full bladder. (IV, C)
  - A leukocyte esterase dipstick on the remains of the FVU specimen may be used to detect urethritis in symptomatic men with a negative urethral smear.<sup>(54)</sup>(IV, C)
- Empirical treatment without verifying the presence of urethritis is not recommended as there is a risk it may perpetuate their symptoms.(IV) This treatment should only be given in exceptional circumstances and their partner(s) should also be treated.

The sensitivity of the smear test for diagnosing urethritis, but probably not the FVU in detecting chlamydia <sup>43,44</sup>, is affected by the period since last passing urine. The optimum time to ensure a definite diagnosis in a symptomatic man is not known, 2-4 hours is conventional. (IV,C)

### **Managing patients in settings in which microscopy is not available**



Symptomatic patients should be strongly encouraged to attend a centre which has microscopy available because the sensitivity and specificity of other methods for diagnosing urethritis is imperfect compared to a urethral smear. When microscopy is not available the following can be used to make a diagnosis of urethritis: (IV, C)

- The presence of a mucopurulent or purulent urethral discharge on examination
- $\geq 1+$  on a leukocyte esterase dipstick on an FVU specimen.(see above)
- The presence of threads in a FVU specimen.<sup>45,46</sup> Threads may be physiological e.g. semen.

### Investigations

- Men assessed for STIs should be tested for *C. trachomatis* from first void urine, regardless of symptoms.
- Men should be tested for *N. gonorrhoeae* if they have a urethritis.
- If *N. gonorrhoeae* or *C. trachomatis* positive, management should be as specified in the European guidelines.
- Testing male patients with urethritis for *M. genitalium*, preferably with screening for macrolide resistance is highly likely to improve clinical outcomes.<sup>47</sup> Testing for *M. genitalium* is therefore recommended.
- In men with symptoms strongly suggestive of a urinary tract infection - for example, severe dysuria, haematuria (microscopic or macroscopic), nocturia, urinary frequency, urgency, or is at low risk for a sexually transmitted infection, a urinary dipstick analysis on a mid-stream urine specimen should be considered and the sample sent for culture and sensitivities.<sup>29</sup> Although a urinary dipstick is only 68-88% sensitive, it is inexpensive and a useful screening test.<sup>29</sup> If a urinary tract infection is confirmed consider further urological assessment. (IV, C)

### GENERAL ADVICE

The following should be discussed and clear written information provided:

- An explanation of the causes of NGU, including non-infective causes, and possible short term and long term implications for the health of the patient and his partner.
- The side effects of treatment
- The importance of:
  - complying with their sex partner(s) being evaluated and treated
  - complying with any follow-up arrangements

- Advice to abstain from sexual intercourse, including for oral sex, until he and his current partner(s) have completed therapy (IV)
- .Advice on safer sex
- .Patient information: <http://iusti.org/regions/Europe/PatientInformation.htm>

## **Treatment**

Men with severe symptoms should be treated as soon as the diagnosis is made and without waiting for the chlamydia, gonorrhoea and *M. genitalium* test results. In men with mild symptoms and microscopically proven low grade urethritis (5-15 PMNLs/hpf), another option is to review the patient after 3-7 days, preferably for an early morning smear, with the results of the NAAT(s) (including *M. genitalium*) and gonorrhoea culture as sometimes urethritis can resolve without treatment.<sup>48</sup> If laboratory tests are positive, or he has persistent microscopic urethritis, microorganism guided antimicrobial treatment can be administered at the second visit.

Ideally, treatment should be effective (microbiological cure >95%), easy to take (twice daily or less), with a low side effect profile, and cause minimal interference with daily lifestyle. However, assessing treatment efficacy is difficult as persistence of inflammation may not indicate persistent infection.<sup>11,49,50</sup> Detectable inflammation may persist for an unknown length of time, even when the putative organism has been eliminated.<sup>51</sup> Two recent large randomised controlled trials from the United States observed that both doxycycline and azithromycin are <85% effective with regard to clinical cure.<sup>13,52</sup>

## **RECOMMENDED REGIMENS (GRADE OF RECOMMENDATION A)**

Doxycycline 100 mgs twice daily (bd) or 200 mgs once daily (od) orally for 7 days (Ib)

## **SECOND LINE REGIMENS (III, C)**

Azithromycin 500 mgs single dose (stat) then 250mgs od for 4 days or Azithromycin 1 gram stat

(Azithromycin 1 gram stat should not be used routinely because of the increased risk of inducing macrolide antimicrobial resistance with *M. genitalium*.<sup>47,53</sup>)

Lymecycline 300mgs bd for 10 days

Tetracycline hydrochloride 500mgs bd for 10 days

If patient is *M. genitalium*-positive

Azithromycin 500 mgs stat, then 250 mgs od for 4 days (see above) (III, C)

- Doxycycline 100 mgs bd for 7 days is > 95% effective in men who are chlamydia-positive,<sup>13,52,54-57</sup> and as effective (70-80%) as azithromycin 1 gram in men who are *U. urealyticum*-positive.<sup>58-60</sup>
- Azithromycin 1 gram is associated with development of macrolide resistance in *M. genitalium*,<sup>13,52,53,61-63</sup> is likely to increase macrolide resistant strains in the population,<sup>47,53,64,65</sup> and has a reduced efficacy in chlamydia-positive men with urethritis.<sup>55,66,67</sup> The efficacy of Azithromycin may be lower than 80% depending on background macrolide resistance in population<sup>47,62,64,68</sup>, and *M. genitalium*-positive men who fail therapy with 1 gram are at high risk of developing a 23sRNA gene mutation conferring macrolide resistance.<sup>53,69-73</sup> If this were to occur, an extended 5 day azithromycin regimen would not be effective at eradicating the infection.<sup>47,64,68,74,75</sup>
- Azithromycin for 5 days (500mgs stat then 250mgs od for 4 days) is about 95% effective in eradicating macrolide susceptible *M. genitalium* and may be more effective at eradicating chlamydia in men with urethritis.<sup>47,67,69,76,77</sup> It appears to induce macrolide antimicrobial resistance at a lower rate than the 1 gram regimen, although there is limited literature evaluating this.<sup>53,69,76</sup> Although macrolide antimicrobial resistance in *M. genitalium* appears to be worldwide and possibly increasing it is probably <40% in the majority of countries.<sup>47,64,65,71,75,78,79</sup>
- *Although never evaluated, using 1gram instead of 500mgs on day 1 maintains the benefits of single dose therapy*, and is likely to improve microbiological cure rates and reduce the risk of macrolide resistance developing in *M. genitalium*. (IV)
- Lyme cycline 300 mgs bd for 10 days or tetracycline hydrochloride 500 mgs bd for 10 days are probably > 95% effective in men who are chlamydia-positive.<sup>80</sup> Unlike doxycycline, these antibiotics do not induce photosensitivity.

### **Sexual contacts/partners**

All sexual partners at risk should be assessed and offered epidemiological treatment, maintaining patient confidentiality. The duration of “look back” is arbitrary; 4 weeks is suggested for symptomatic men. Partner(s) notification and management should be carried out with sensitivity, considering socio-cultural issues and avoiding stigma.

Current partner(s) should be tested and treated and the patient advised not to be sexually active until all have completed treatment.

If *C. trachomatis* or *N. gonorrhoeae* are detected it is important to ensure that all sexual partner(s) potentially at risk have been notified and managed as detailed in the European Chlamydia and Gonorrhoea guidelines.

(available at <http://www.iusti.org/regions/europe/euroguidelines.htm>)

- Details of all contacts should be obtained at the first visit. Consent should also be obtained so that if *C. trachomatis*, *N. gonorrhoeae*, or *M. genitalium* are detected subsequently and the index patient does not re-attend, he can be contacted and/or provider referral can be initiated for sexual contacts (IV, C).

In a study conducted before NAAT for *C. trachomatis* and *M. genitalium* was available there was no evidence of treatment benefit to partners of men with chlamydia-negative NGU.<sup>81</sup> There are, however, a number of issues which may influence decision making.

- *M. genitalium* accounts for approximately 15-30% of cases and there is a high concordance of infection in sexual partners.<sup>82</sup> *M. genitalium* probably causes disease in women and is a co-factor in HIV transmission.<sup>14,47,83</sup>
- There are reports of patients with persistent or recurrent ureaplasma-positive urethritis being cured only after their sexual partner received appropriate treatment.<sup>84</sup>

### **Follow up for patients with NGU**

Patients with persistence of any symptoms however slight at three weeks should be asked to return to the clinic and if confirmed persistent urethritis retreated with appropriate regimen (see below) and the possibility of re-infection explored. (IV, C) A test of cure 3-4 weeks after treatment in those who tested positive for *M. genitalium* should be performed<sup>85</sup>.

If chlamydia is confirmed (see European guideline), a test of cure is not recommended to be routinely performed in uncomplicated urethritis.

### **Persistent and recurrent NGU**

Persistent NGU, when symptoms do not resolve following treatment, can result from both treatment failure and re-infection. It occurs in 15-25% of patients following initial treatment of acute NGU. Recurrent NGU is empirically defined as the recurrence of symptomatic

urethritis occurring 30-90 days following treatment of acute NGU<sup>11</sup> and occurs in 10-20% of patients.<sup>11,86</sup>

The aetiology of persistent NGU is probably multifactorial with an infectious agent being identified in <50% of cases.<sup>6,11,74,86</sup> *M. genitalium* has been identified in 20-40%<sup>6,11,74,87</sup> and *C. trachomatis* in 10%-20% of men treated with azithromycin 1gram.<sup>52</sup> *U. urealyticum* may also play a role in some men, but urethritis appears to resolve despite persistent infection.<sup>11,58,60,88</sup> *Trichomonas vaginalis* can be identified in up to 10% of populations where it is endemic.<sup>6</sup> Herpes simplex virus should also be considered as this can cause dysuria without signs outside the urethra.

Any treatment of persistent NGU should cover *M. genitalium*, *T. vaginalis* and probably BV associated bacteria.<sup>25,28,89</sup> The only randomised controlled trial for persistent NGU was undertaken before *M. genitalium* had been identified as an important pathogen (but before macrolide resistance was common) and used erythromycin, an older generation macrolide.<sup>90</sup> Although a 3 week course was better than placebo it is not clear how relevant this regimen is today, given that better macrolides are available with less side effects.<sup>91</sup>

It is likely that re-treatment of the sexual partner and index case will be beneficial if persistent/recurrent NGU in the index case resolves following extended therapy, but subsequently recurs. This remains an area where further research is needed. (IV, C)

#### DIAGNOSIS OF PERSISTENT/RECURRENT NGU (IV, C)

- Only undertake a Gram or methylene blue stained urethral smear in men who are symptomatic.
- For those patients with confirmed chlamydia at initial presentation please refer to European Chlamydia guideline for further guidance on repeat NAAT testing.
- Test for *M. genitalium* using a NAAT, including screening for macrolide resistance if not undertaken at presentation.
- Consider testing for *Trichomonas vaginalis* using a NAAT if available, if it is prevalent (>2% in symptomatic women) in the local population.

#### RECOMMENDED REGIMENS – second attendance or first follow-up visit

Patient symptomatic or an observable discharge present AND microscopic evidence of urethritis. <sup>11,14,50,69,92</sup>

### **Doxycycline prescribed as first line therapy**

Azithromycin 500 mgs then 250mg for the next 4 days (III, B)

plus metronidazole 400 mgs twice daily for 5 days (IV, C)

NB if macrolide resistant *M. genitalium* is detected moxifloxacin should be substituted for azithromycin (see below)

### **Azithromycin prescribed first line therapy**

Moxifloxacin 400 mgs orally once daily for 7-14 days (III, B)

plus metronidazole 400 mgs twice daily for 5 days (IV, C)

NB: moxifloxacin should be used with caution and reserved for treatment failures which are thought secondary to macrolide resistant *M. genitalium*, because of rare but serious adverse reactions. Australia successfully uses a 10 day course and Nordic countries a 7 day course whilst no treatment failures have been identified using a 14 day regimen in the UK. <sup>47,69,93,94</sup>. However a recent study suggests a 14 day course is more effective than a seven day course in eradicating *M. genitalium* in women with cervicitis.<sup>95</sup> In patients having contracted *M. genitalium* infection in South-East-Asia, dual resistance to both macrolides and fluoroquinolones are currently around 10%. Such infections are difficult to treat and only pristinamycin (registered in France) has proven effective on a case basis.<sup>75</sup>

## **CONTINUING SYMPTOMS**

There is only limited evidence on how best to manage patients who either remain symptomatic following a second course of treatment, or who have frequent recurrences after treatment. Testing for *M. genitalium* is essential to guide management.

- Moxifloxacin 400mgs orally once daily for 7-14 days (IIIb, B)
- Urological investigation is usually normal unless the patient has urinary flow problems <sup>96,97</sup> and is not recommended. (IV, C)

- The chronic pelvic pain syndrome should be considered in the differential diagnosis.<sup>90,98,99</sup>

Table 1. Prevalence of the most common pathogens isolated from patients with NGU

Micro-organism	Prevalence	Reference
<i>C. trachomatis</i>	11-50%	3,4,6,8,10-13,19,23,52,100-107
<i>M. genitalium</i>	6-50%	3-6,8,11,13,16,19,23,52,79,102,104-108
Ureaplasmas	5-26%	3,11,13,23,104,106,107,109,110
<i>T. vaginalis</i>	1-20%	3,6,19,52,107,111-113
<i>Adenoviruses</i>	2-4%	8,30
<i>Herpes simplex virus</i>	2-3%	8,114

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([http://www.iusti.org/regions/Europe/pdf/2013/Editorial\\_Board.pdf](http://www.iusti.org/regions/Europe/pdf/2013/Editorial_Board.pdf))

### Potential or perceived conflicts of interest

PH reports personal fees from Aquarius Population Health, grants, personal fees and non-financial support from Cepheid, personal fees from Crown Prosecution Service, personal fees from British Association for Sexual Health and HIV, grants from Mast Group Ltd, grants and personal fees from Hologic, outside the submitted work; In addition, PH has a patent "A sialidase spot test to diagnose bacterial vaginosis" issued to University of Bristol.

HM has received a honorarium and travel expenses from Becton Dickinson for a lecture on *Mycoplasma genitalium*



KB, LF, and WvdM none reported

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